Exhibit A

Structure task started on Thu Mar 22, 2007 at 12:04 PM

Get substances that match this structure by substructure search
Explored by Chemical Substructure in REGISTRY.
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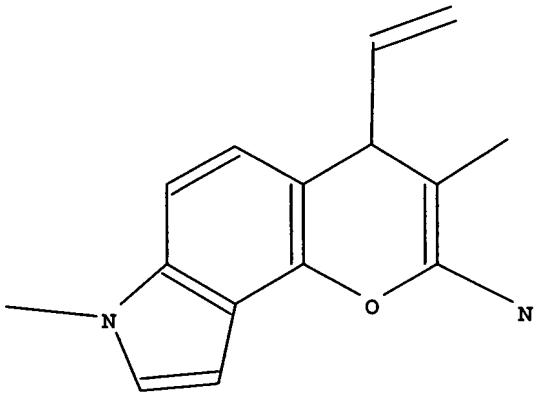

45 Substances

Get References started

4 references were found for 45 of 45 substances in CAPLUS

4 references were found (0 duplicates removed)

Bibliographic Information

Preparation of substituted 4-aryl-4H-pyrrolo[2,3-h]chromenes and analogs as activators of caspases and inducers of apoptosis and their uses against cancer and other disorders.

Cai, Sui Xiong; Jiang, Songchun; Kemnitzer, William E.; Zhang, Hong; Attardo, Giorgio; Denis, Real. (Cytovia, Inc., USA; Shire Biochem, Inc.). PCT Int. Appl. (2003), 110 pp. CODEN: PIXXD2 WO 2003097806 A2 20031127 Designated States W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW. Designated States RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG. Patent written in English. Application: WO 2003-US15427 20030516. Priority: US 2002-378079 20020516. CAN 140:5049 AN 2003:931479 CAPLUS (Copyright (C) 2007 ACS on SciFinder (R))

Patent Family Information

Patent No.	Kind	Date	Application No.	Date
WO 2003097806	A2	20031127	WO 2003-US15427	20030516
WO 2003097806	A3	20040930		
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AU 2003230411	A1	20031202	AU 2003-230411	20030516
EP 1509515	A2	20050302	EP 2003-724599	20030516
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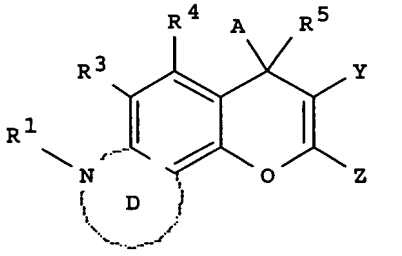
CN 1668609	A	20050914	CN 2003-816725	20030516
JP 2005531566	T	20051020	JP 2004-506465	20030516
US 2006104998	A1	20060518	US 2004-514427	20041116

Priority Application		
US 2002-378079P	P	20020516
WO 2003-US15427	W	20030516

Abstract

The present invention is directed to substituted 4-aryl-4H-pyrrolo[2,3-h]chromenes and analogs thereof (shown as I; variables defined below; e.g. II). The present invention also relates to the discovery that compds. I are activators of caspases and inducers of apoptosis. Therefore, I can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs. The ability to activate the caspase cascade and induce apoptosis in human breast cancer cell lines T-47D and ZR-75-1 was measured for .apprx.50 examples of I, e.g. EC50 (nM) = 2.3 and 1.6, resp., for II. Although the methods of prepn. are not claimed, .apprx.50 example prepns. are included. For I: R1 = alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, aminoalkyl and oxiranylalkyl; R3 and R4 = H, halo, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, C1-10 alkyl, alkenyl,

alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, carbonylamido or alkylthio; R5 is H or C1-10 alkyl. A is (un)substituted and is aryl, heteroaryl, satd. carbocyclic, partially satd. carbocyclic, satd. heterocyclic, partially satd. heterocyclic or arylalkyl; D is (un)substituted and is a heteroarom., partially satd. (un)satd. heterocyclic fused ring, wherein said fused ring has 5 or 6 ring atoms, wherein one or two of said ring atoms are N atoms and the others of said ring atoms are C atoms. Y is CN, COR19, CO2R19 or CONR20R21, wherein R19, R20 and R21 = H, C1-10-alkyl, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl or aminoalkyl; or R20 and R21 are taken together with the N to form a heterocycle; and Z is NR22R23, NHCOR22N(COR23)2, N(COR22)(COR23), N:CHOR19 or N:CHR19 wherein R22 and R23 = H, C1-4 alkyl or aryl, or R22 and R23 are combined together with the group attached to them to form a heterocycle.



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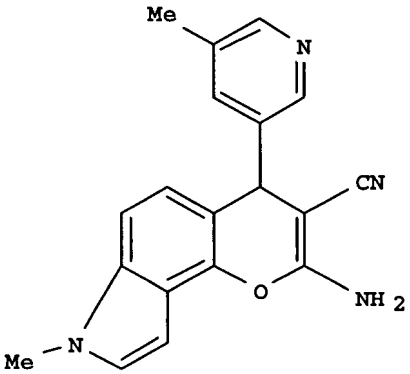

II

Bibliographic Information

Preparation of substituted 4H-chromenes, 2H-chromenes, chromans and analogs as activators of caspases and inducers of apoptosis and their uses against cancer and other disorders. Cai, Sui Xiong; Jiang, Songchun; Attardo, Giorgio; Denis, Real; Storer, Richard; Rej, Rabindra. (Cytovia, Inc., USA; Shire Biochem, Inc.). PCT Int. Appl. (2003), 116 pp. CODEN: PIXXD2 WO 2003096982 A2 20031127 Designated States W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW. Designated States RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG. Patent written in English. Application: WO 2003-US15432 20030516. Priority: US 2002-378043 20020516. CAN 140:5041 AN 2003:931119 CAPLUS (Copyright (C) 2007 ACS on SciFinder (R))

Patent Family Information

Patent No.	Kind	Date	Application No.	Date
WO 2003096982	A2	20031127	WO 2003-US15432	20030516
WO 2003096982	A3	20040729		

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EP 1513515	A2	20050316	EP 2003-731218	20030516
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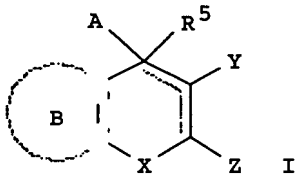
US 2005176750	A1	20050811	US 2003-514426	20030516

Priority Application

US 2002-378043P	P	20020516
WO 2003-US15432	W	20030516

Abstract

The present invention is directed to substituted 4H-chromenes, 2H-chromenes, chromans and analogs thereof (shown as I; variables defined below; e.g. II). The present invention also relates to the discovery that compds. I are activators of caspases and inducers of apoptosis. Therefore, I can be used to induce cell death in a variety of clin. conditions in which uncontrolled growth and spread of abnormal cells occurs. The ability to activate the caspase cascade and induce apoptosis in human breast cancer cell lines T-47D and ZR-75-1 was measured for .apprx.30 examples of I, e.g. EC50 (nM) = 2.7 and 2.2, resp., for II. Although the methods of prepn. are not claimed, .apprx.30 example prepns. are included. For I: X is O, S or NR6, wherein R6 is H or (un)substituted alkyl; Y is H, halogen, CN, COR7, CO2R7 or CONRxRy, wherein R7, Rx and Ry = H, C1-10-alkyl, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl or aminoalkyl; or Rx and Ry are taken together with the N to which they are attached to form a heterocycle. Z is H, OH, OR8, OCOR8, wherein R8 is H, C1-10 alkyl, haloalkyl, aryl, fused aryl, carbocyclic, a heterocyclic group, a heteroaryl group, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl or aminoalkyl, when the dotted line between C atoms bonded to groups Y and Z is not present Z can be dialkyl. R5 is H or C1-10-alkyl; A is (un)substituted and is aryl, heteroaryl, satd. carbocyclic, partially satd. carbocyclic, satd. heterocyclic, partially satd. heterocyclic, arylalkyl or heteroarylalkyl; B is an (un)substituted arom. or heteroarom. ring;
and the dotted lines are single or double bonds, provided that both sets of dotted lines cannot be double bonds at the same time and R5 is not present when the dotted line between C atoms bonded to groups A and Y is a double bond.



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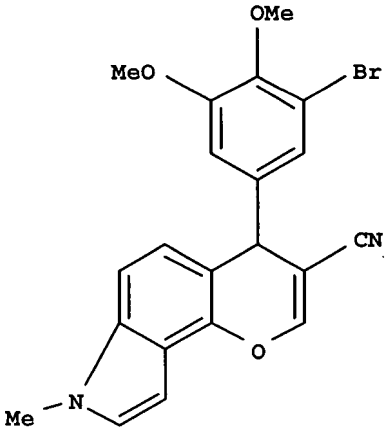

II

Bibliographic Information

Preparation of substituted 4H-chromenes and analogs as activators of caspases and inducers of apoptosis and their uses against cancer and other disorders. Cai, Sui Xiong; Zhang, Hong; Jiang, Songchun; Storer, Richard. (Cytovia, Inc., USA). PCT Int. Appl. (2002), 139 pp. CODEN: PIXXD2 WO 2002092594 A1 20021121 Designated States W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW. Designated States RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG. Patent written in English. Application: WO 2002-US15399 20020516. Priority: US 2001-290997 20010516. CAN 137:369971 AN 2002:888735 CAPLUS (Copyright (C) 2007 ACS on SciFinder (R))

Patent Family Information

Patent No.	Kind	Date	Application No.	Date
WO 2002092594	A1	20021121	WO 2002-US15399	20020516
WO 2002092594	A8	20040624		
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US 2003065018	A1	20030403	US 2002-146138	20020516
US 7053117	B2	20060530		
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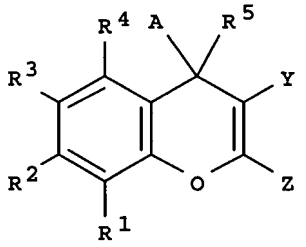
CN 1516700	A	20040728	CN 2002-812067	20020516
JP 2004530692	T	20041007	JP 2002-589478	20020516
US 2006035925	A1	20060216	US 2005-150586	20050613

Priority Application

US 2001-290997P	P	20010516
WO 2002-US15399	W	20020516
US 1999-163584P	P	19991105
US 2000-185211P	P	20000224
US 2000-705840	A2	20001106
US 2002-146138	A1	20020516

Abstract

The present invention is directed to substituted 4H-chromenes and analogs thereof (shown as I; e.g. 2-amino-3-cyano-7-hydroxy-4-(3-bromo-4,5-dimethoxyphenyl)-4H-chromene). It also relates to the discovery that I are activators of caspases and inducers of apoptosis and, therefore, can be used to induce cell death in a variety of clin. conditions in which controlled growth and spread of abnormal cells occurs. In I: R1-R4 = H, halo, haloalkyl, aryl, fused aryl, carbocyclic, heterocyclic, heteroaryl, C1-10 alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, nitro, amino, cyano, acylamido, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, methylenedioxy, carbonylamido or alkylthio; or R1 and R2, or R2 and R3, or R3 and R4, taken together with the atoms to which they are attached form an aryl, heteroaryl, partially satd. carbocyclic or partially satd. heterocyclic group, wherein said group is optionally substituted. R5 is H or C1-10 alkyl; A is optionally substituted and is aryl, heteroaryl, satd. carbocyclic, partially satd. carbocyclic, satd. heterocyclic, partially satd. heterocyclic or arylalkyl; Y is CN, COR7, CO2R7 or CONRxRy, wherein R7, Rx and Ry = H, C1-10 alkyl, haloalkyl, aryl, fused aryl, carbocyclic, heterocyclic, heteroaryl, alkenyl, alkynyl, arylalkyl, arylalkenyl, arylalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, carbocycloalkyl, heterocycloalkyl, hydroxyalkyl or aminoalkyl; or Rx and Ry are taken together with the N to which they are attached to form a heterocycle; and Z is NR8R9, NHCOR8, N(COR9)2, N(COR8)(COR9), N:CHOR8 or N:CHR8, wherein R8 and R9 = H, C1-4 alkyl or aryl, or R8 and R9 are combined together with the group attached to them to form a heterocycle. The EC50 values for >80 I against T-47D and ZR-75-1 human breast cancer cell lines are tabulated, e.g.
30 and 25 nM, resp., for 2-amino-3-cyano-4-(3-bromo-4,5-dimethoxyphenyl)-4H-indolo[7,6-b]pyran. Although the methods of prepn. are not claimed, 81 example prepns. are included.



I

Bibliographic Information

Preparation of substituted coumarins and quinolinones as caspase activators for treatment of cancer. Cai, Sui Xiong; Zhang, Hong; Kemmitzer, William E.; Jiang, Songchun; Drewe, John A.; Storer, Richard. (Cytovia, Inc., USA; Shire Biochem, Inc.). PCT Int. Appl. (2002), 84 pp. CODEN: PIXXD2 WO 2002092076 A1 20021121 Designated States W: AE,

AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM. Designated States RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, ML, MR, NE, SN, TD, TG. Patent written in English. Application: WO 2002-US15401 20020516. Priority: US 2001-290978 20010516. CAN 137:384750 AN 2002:888548 CAPLUS (Copyright (C) 2007 ACS on SciFinder (R))

Patent Family Information

Patent No.	Kind	Date	Application No.	Date
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US 2003114485	A1	20030619	US 2002-146136	20020516
US 7015328	B2	20050321		
EP 1392283	A1	20040303	EP 2002-731803	20020516
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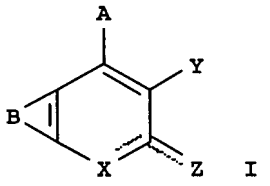
US 2005090526	A1	20050428	US 2004-989057	20041116

Priority Application		
US 2001-290978P	P	20010516
WO 2002-US15401	W	20020516
US 2002-146136	A3	20020516

Abstract

Title compds. I [wherein X = O, S or NR6; R6 = H or (un)substituted alkyl or aryl; Y = CN, COR7, CO2R7, or CONR9R10; R7, R9, and R10 = independently H, (halo)alkyl, (fused) aryl, carbocyclyl, heterocyclyl, heteroaryl, alkenyl, alkynyl, (hetero)arylalkyl, (hetero)arylalkenyl, (hetero)arylalkynyl, (hetero)cycloalkyl, hydroxyalkyl, or aminoalkyl; or NR9R10 = heterocyclyl; Z = O, S, halo, NR8, or NCOR8; R8 = independently H, alkyl, or aryl; A = (un)substituted (hetero)aryl, (hetero)cyclyl, or (hetero)arylalkyl; B = (un)substituted (hetero)aryl or (hetero)cyclyl; or pharmaceutically acceptable salts or prodrugs thereof] were prepd. as caspase activators and inducers of apoptosis. For example, condensation of 5-bromoveratraldehyde with Et cyanoacetate in EtOH in the presence of piperidine gave 3-(3-bromo-4,5-dimethoxyphenyl)-2-cyanoacrylic acid Et ester. Treatment of the acrylate with a soln. of 3-methoxyphenol and NaH in toluene afforded the coumarin II (1.7%). The latter induced apoptosis in the human breast cancer cell lines T-47D and ZR-75-1 with EC50 values of 257 nM and 97 nM, resp. Therefore, I, optionally administered with at least one known cancer chemotherapeutic agent, are useful for the treatment of cancer.



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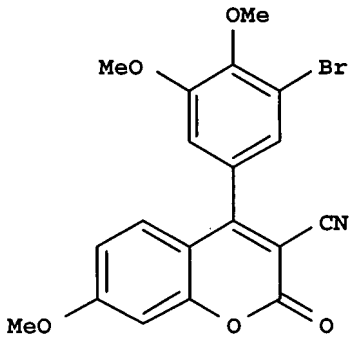

II